IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Christopher Eckman et al.   Art Unit : 1646
Serial No. : 09/824,924   Examiner : O. Chernyshev
Filed : April 3, 2001
Title : ENDOTHELIN CONVERTING ENZYMES AND THE AMYLOID BETA
PEPTIDE

RECEIVED

U.S. Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202

NOV 2 5 2002

TECH CENTER 1600/2900

RESPONSE

In response to the Office Action mailed July 15, 2002, please amend the application as follows:

In the Specification:

Please replace the paragraph on page 12, lines 10-27 with the following:

--Site-directed mutagenesis previously has been performed on ECEs, as well as on related zinc metalloendopeptidases (*e.g.,* neprilysin (NEP), thermolysin) to identify important residues (see Shimada et al., 1996, *Biochem J.*, 315:863-7; Hoang et al., 1997, *Biochem J.*, 327:925-9; Savage et al., 1998, *J. Cardiovasc. Pharmacol.*, 31(Suppl.):S16-18; Marie-Claire et al., 1999, *J. Mol. Biol.*, 285:1911-5). A typical ECE-1, for example, has a short N-terminal tail (about 50 residues), one or more hydrophobic transmembrane domains (usually about 20 residues) and a large domain that includes a zinc-binding motif common to catalytic domains of metalloproteases (about 680 residues). The residues acting as zinc ligands and those involved in the catalytic activity are known, and include two histidines (H) that bind zinc and are very close together in the sequence, and an active site glutamic acid (E) residue C-terminal to the first histidine that acts as a nucleophile and promotes the attack on the carbonyl carbon of the substrate by a water molecule. The consensus pattern for ECE enzymes is as follows: